


Association of Obstructive Sleep Apnea with Nonalcoholic Fatty Liver Disease: Evidence, Mechanism, and Treatment

Lingling Wang¹, Huiguo Liu¹, Ling Zhou¹, Pengdou Zheng¹, Hai Li^{2,3}, Huojun Zhang^{4,*}, Wei Liu^{2,3,*}

¹Department of Respiratory and Critical Care Medicine, Key Laboratory of Pulmonary Diseases of Health Ministry, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China; ²Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China; ³Key Laboratory of Vascular Aging, Ministry of Education, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China; ⁴Department of Respiratory and Critical Care Medicine, Renmin Hospital of Wuhan University, Wuhan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Huojun Zhang, Email hjzhang@whu.edu.cn; Wei Liu, Email 404793938@tjh.tjmu.edu.cn

Abstract: Obstructive sleep apnea (OSA), a common sleep-disordered breathing condition, is characterized by intermittent hypoxia (IH) and sleep fragmentation and has been implicated in the pathogenesis and severity of nonalcoholic fatty liver disease (NAFLD). Abnormal molecular changes mediated by IH, such as high expression of hypoxia-inducible factors, are reportedly involved in abnormal pathophysiological states, including insulin resistance, abnormal lipid metabolism, cell death, and inflammation, which mediate the development of NAFLD. However, the relationship between IH and NAFLD remains to be fully elucidated. In this review, we discuss the clinical correlation between OSA and NAFLD, focusing on the molecular mechanisms of IH in NAFLD progression. We meticulously summarize clinical studies evaluating the therapeutic efficacy of continuous positive airway pressure treatment for NAFLD in OSA. Additionally, we compile potential molecular biomarkers for the co-occurrence of OSA and NAFLD. Finally, we discuss the current research progress and challenges in the field of OSA and NAFLD and propose future directions and prospects.

Keywords: intermittent hypoxia, hypoxia-inducible factor 1 alpha, nonalcoholic fatty liver disease, oxidative stress, dyslipidemia, leptin resistance

Introduction

Obstructive sleep apnea (OSA) is common in the general population and is characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep, resulting in periods of intermittent hypoxia (IH), snoring, and sleep fragmentation (SF).¹ OSA is increasingly recognized as a multisystem disorder because of its association with multiple adverse health outcomes, including cardiovascular and metabolic diseases.² Nocturnal polysomnography (PSG) is the preferred method for diagnosing OSA. This test should report an apnea/hypopnea index (AHI), which is the sum of apneas (cessation of respiratory airflow for >10 s) and hypopneas (characterized by at least a 30% reduction in airflow for >10 s associated with oxygen desaturation or arousal on electroencephalogram) per hour of sleep.³ The severity of OSA is assessed using the AHI and described as mild (5–14.9), moderate (15–29.9), and severe (≥ 30).⁴ The prevalence of OSA, defined by an AHI of more than five events per hour, has increased significantly over the past few decades.^{5,6} In Lausanne, the prevalence of moderate-to-severe OSA (AHI ≥ 15 /h) was 23.4% in women and 49.7% in men.⁵ Furthermore, a recent study showed that the prevalence of mild-to-severe sleep-disordered breathing (SDB) was 43.2%, moderate-to-severe SDB was 11.6%, and severe SDB (AHI ≥ 30 /h) was 2.7% in 1810 participants with complete respiratory polygraphic data.⁷ Furthermore, the economic costs associated with sleep disorders (including OSA) are substantial.⁸

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease condition characterized by the accumulation of lipid droplets in >5% of hepatocytes.⁹ NAFLD has become an important global public health problem, with obesity being the major risk factor. The global prevalence of NAFLD in the general population is approximately 25%, reaching even 90% in the morbidly obese patient population and increasing with the prevalence of obesity.^{10,11} The first stage of NAFLD is characterized by simple steatosis, followed by further liver deterioration leading to overt steatohepatitis (nonalcoholic steatohepatitis [NASH]), which is characterized by steatosis, hepatocyte ballooning, and inflammatory infiltration. NASH may be followed by the development of fibrosis, liver cirrhosis, liver failure, and possibly hepatocellular carcinoma.^{12,13}

The independent risk factors for OSA include advanced age, male sex, large neck circumference, abdominal obesity, being overweight or obese, and snoring.^{7,14} OSA, a metabolic-related disease, is a risk factor for many metabolic diseases through IH mediation in the general population, such as type 2 diabetes mellitus and cardiovascular and cerebrovascular diseases, particularly NAFLD.^{15–17} Increasing evidence links the severity of OSA with the occurrence and progression of NAFLD, particularly concerning the impact of moderate-to-severe OSA on the development of NAFLD. A recent review summarized the many related links between OSA and NAFLD, focusing on describing the evidence and some mechanisms linking OSA to NAFLD.¹⁸ However, based on some clinical studies, the therapeutic efficacy of continuous positive airway pressure (CPAP), a classic method for treating OSA, for NAFLD remains controversial, and there is currently a lack of comprehensive reviews summarizing this aspect. Therefore, this review focuses on introducing recent and comprehensive molecular mechanisms and screening indicators of NAFLD combined with OSA and summarizing clinical studies on the effectiveness of CPAP treatment for NAFLD.

Clinical Evidence Linking OSA to NAFLD

Clinical Evidence

Increasing clinical evidence has shown the association of OSA with the presence and severity of NAFLD, particularly in adults.^{17,19,20} An observational study involving 334 patients showed that the severity of OSA evaluated with AHI was associated with a decrease in transaminase levels, high-density lipoprotein levels, body mass index (BMI), homeostatic model assessment for insulin resistance (HOMA-IR) index, and fibrosis-4 index (FIB-4), demonstrating sufficient sensitivity and specificity for the degree of fibrosis.²¹ Similarly, AHI was reported as an independent predictor of significant fibrosis in NAFLD patients with OSA.²² Moreover, in patients with metabolic comorbidities, severe OSA was independently associated with increased liver stiffness, evaluated via liver stiffness measurement, which can help diagnose the stage of liver fibrosis.²³ Furthermore, a multisite cross-sectional study of 1285 patients reported that the risk of hepatic steatosis, but not hepatic fibrosis, increased with OSA severity and sleep-related hypoxemia, adjusted for confounders, including central obesity.²⁴ Additionally, a meta-regression analysis of nine studies (2272 participants) found that OSA was associated with steatosis, lobular inflammation, ballooning degeneration, and fibrosis. The severity of OSA was also associated with ALT levels but not AST levels.²⁵ Moreover, another meta-analysis involving 18 cross-sectional studies (2183 participants) found that OSA was associated with the severity and prevalence of NAFLD, NASH, and fibrosis, independent of age, sex, BMI, and abdominal obesity.²⁶

There are many common risk factors for OSA and NAFLD, including male sex, older age, and obesity.²⁷ Additionally, OSA seems to affect the severity of NAFLD after adjusting for these common risk factors. OSA severity is directly correlated with NAFLD severity, and OSA may lead to a higher risk of NASH in obese patients, which remains statistically significant after adjusting for BMI and other related factors.^{17,28,29} In short, the presence and severity of OSA are closely related to the histological elements of NAFLD, including the steatosis degree, lobular inflammation, and fibrosis stage.

Some studies have shown that OSA is associated with the presence and severity of NAFLD in children. In one study, OSA affected 60% of 65 children with biopsy-proven NAFLD, and the presence and severity of OSA were associated with features of NASH and fibrosis, similar to those observed in nonobese children with NAFLD.³⁰ Similarly, pediatric obese or nonobese adolescents with NAFLD who had OSA/hypoxia showed more severe fibrosis than their non-OSA/hypoxia counterparts.^{31,32} The hypoxia and hedgehog pathways were activated in pediatric NAFLD patients with OSA

and associated with disease severity.³³ Moreover, a previous meta-analysis also demonstrated that OSA is associated with NAFLD, as the OSA group had higher liver enzyme levels and progressive liver fibrosis than the control group in the pediatric population.³⁴ In summary, OSA is associated with NAFLD progression not only in adults but also in children.

Effect of CPAP

CPAP helps people breathe during sleep by providing adjustable air pressure through a mask or nosepiece. Generally, OSA is associated with metabolic comorbidities, and CPAP treatment can improve many metabolic diseases, including diabetes^{35,36} and hypertension.^{37,38} Does CPAP improve NAFLD in OSA patients? There are several studies on whether CPAP improves the clinical features of NAFLD in patients with OSA and NAFLD ([Table S1](#)). However, few randomized controlled trials have succeeded in demonstrating a clinical effect of CPAP on noninvasive markers of NAFLD severity. In the largest such study of CPAP effects in NAFLD/OSA, Ng et al's randomized clinical trial involving 120 patients, a 6-month CPAP intervention did not lead to improvements in hepatic steatosis and fibrosis among NAFLD patients with OSA.³⁹ However, a main weakness of the study was that the "sham CPAP" group had a large reduction in respiratory event index. Therefore, it is difficult to conclude that the failure to demonstrate a significant difference between CPAP and sham CPAP is due to a lack of effect of CPAP versus a significant effect of subtherapeutic CPAP.

The results of studies on the efficacy of different CPAP treatments for NAFLD have been variable ([Table S1](#)). There may be several reasons for these discrepant findings. First, the studies employed different approaches for diagnosing NAFLD. Pathological and histological features are critical for NAFLD management, and the degree of steatosis and fibrosis may affect the treatment difficulty. Moreover, the parameters used to assess NAFLD severity vary. There is no doubt that the diagnostic approach and severity classification have a significant impact on treatment outcomes. Additionally, one of the limitations of some studies is the lack of clear division of OSA classification in terms of treatment, which may contribute to inconsistent treatment effects. Second, CPAP compliance was not well-controlled in some studies. High-quality, accurate use of CPAP is important, as is the duration of use each night. Moreover, the duration of the entire trial is also critical in determining the effect. In general, the longer the use, the better and more reliable the results. More importantly, confounding factors (eg, high BMI) need to be corrected to increase the reliability of the evidence.

In Conclusion, whether CPAP improves NAFLD in OSA patients remains inconclusive. These studies have not definitively demonstrated whether the relationship between OSA and NAFLD is causal or merely associative, and there is currently no clear evidence. It is possible that OSA and NAFLD mutually exacerbate each other and contribute to their development. Alternatively, they may represent different outcomes resulting from common features such as obesity and metabolic abnormalities. It is also possible that they indeed have unknown causal relationships. Given the current mixed results of the studies, future research is needed to improve compliance with CPAP use, extend follow-up periods, and increase the sample size to provide more convincing evidence of the effect of CPAP in NAFLD cases.

Possible Mechanisms Linking IH to NAFLD

OSA may cause pathological changes in cells and the body through various mechanisms ([Figure 1](#)). As mentioned previously, IH and sleep disorders, which are characteristics of OSA, play important roles in OSA and NAFLD pathogenesis.¹⁷ IH induces tissue hypoxia, which increases the expression of hypoxia-inducible factor 1 alpha (HIF-1 α) and downstream genes involved in oxidative stress, inflammation, lipogenesis, and overactivation of the sympathetic nervous system, thereby leading to proinflammatory cytokine overproduction, vascular endothelial dysfunction, pancreatic beta cell injury, metabolic dysregulation, and insulin resistance (IR). Oxidative stress, inflammation, IR, and lipid metabolism disorders are key factors in OSA and NAFLD physiopathology ([Figure 2](#)). Although IH is the main mediator of the increased risk of NAFLD induced by OSA, SF also plays an important role in NAFLD onset and development.

IH and Oxidative Stress

NAFLD is strongly associated with oxidative stress.^{40,41} IH and subsequent reoxygenation lead to the production of reactive oxygen species (ROS), resulting in systemic oxidative stress in OSA patients.^{42,43} IH remodels hepatic mitochondrial structure and function through increased hepatic DNA damage and ROS production, leading to an

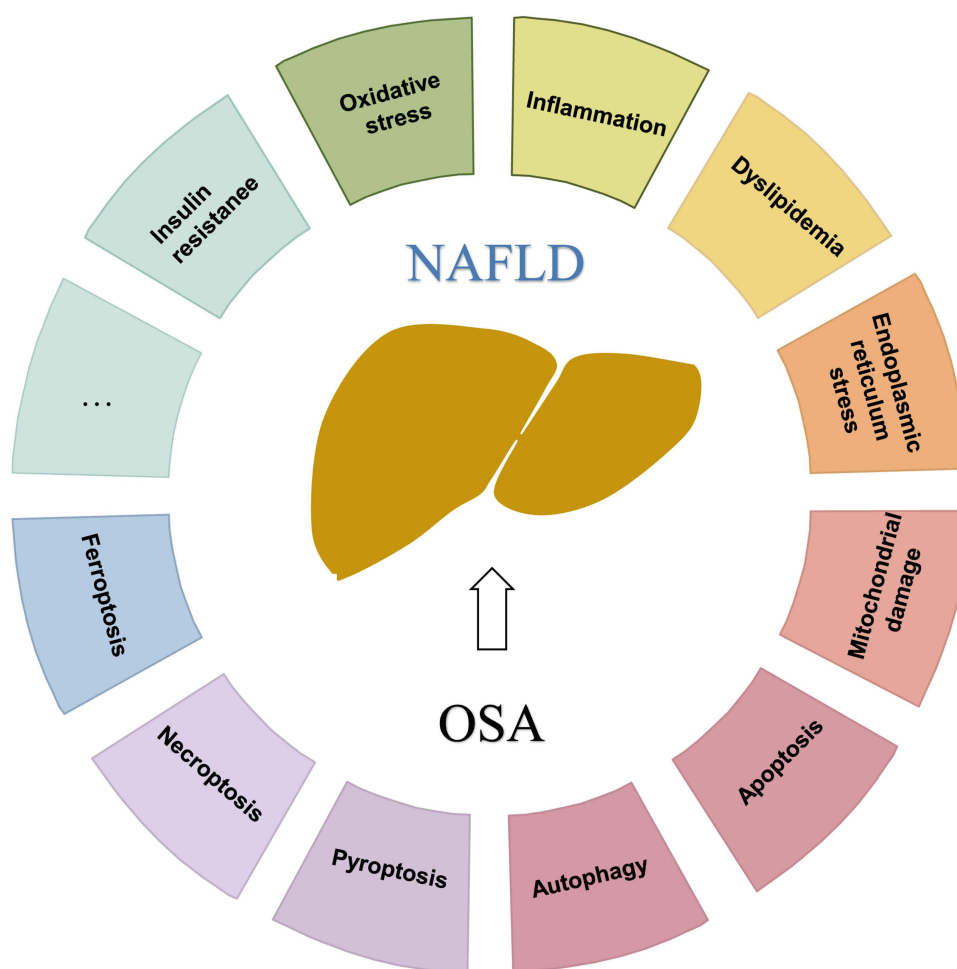


Figure 1 Obstructive sleep apnea (OSA) may cause pathological changes in cells and the body through various mechanisms. The characteristics of OSA, such as intermittent hypoxia, sleep fragmentation, and poor sleep quality, may cause pathological changes in cells and the body through various mechanisms.

imbalance between oxidative stress and antioxidant defense. This effect was observed in mice directly exposed to 2 weeks of IH, simulated with 1-min cycles alternating 30s of hypoxia (5% FiO₂) and 30s of normoxia (21% FiO₂), which serves as a more appropriate simulation of OSA patients.⁴⁴

The hypoxia signaling pathway likely plays a significant role in the contribution of IH to oxidative stress in NAFLD.^{45,46} HIFs, comprising hypoxia-dependent α -subunits (including HIF-1 α , HIF-2 α , and HIF-3 α) and a common constitutively expressed β -subunit, serve as master regulators of oxygen homeostasis by activating the transcription of target genes. Although the regulation and function of HIF-1 α and HIF-2 α are well established, those of HIF-3 α remain less understood.^{47,48} Extensive evidence supports the association between elevated HIF-1 α levels and NAFLD development, emphasizing its role in regulating oxidative stress, immunity, and inflammation.^{49,50} Emerging evidence suggests that IH increases HIF-1 α protein expression and transactivation, leading to various biological and pathophysiological changes in OSA.^{47,51,52} Although there are fewer clinical studies on HIF-1 α levels in NAFLD patients with OSA, several studies have indicated that IH mediates HIF-1 α to exacerbate inflammation and liver fibrosis in NAFLD mouse models.^{53,54} In IH mouse models simulated via intraperitoneal injection of sodium nitrite, HIF-1 α protein levels increased, impacting the Treg/Th17 balance and accelerating the development of NASH and fibrosis. Interestingly, these conditions were ameliorated by HIF1 α siRNA treatment.⁵³ Another study highlights the key role of HIF-1 α in liver fibrosis development, angiogenesis, and inflammatory factors, demonstrating improvement through HIF-1 α intervention in rats with NASH and IH treated with sodium nitrite (NaNO₂).⁵⁴ The mechanism suggests that IH, as a systemic

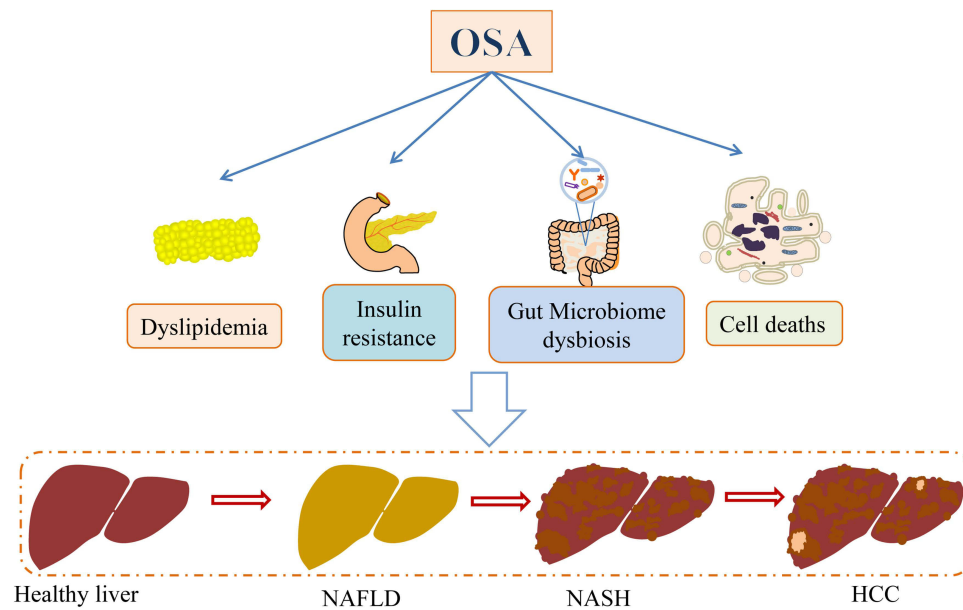


Figure 2 Role of obstructive sleep apnea (OSA) in NAFLD development and progression. In general, OSA may lead to lipid metabolism impairment, insulin resistance, gut microbiota dysregulation, and various liver cell death mechanisms (such as apoptosis, pyroptosis, and ferroptosis), thereby participating in NAFLD occurrence and development.

stimulus, induces HIF-1 α , placing the body in a state of oxidative stress and inflammation, recognized for its role in the development of liver fibrosis in NAFLD.⁵⁵

The endoplasmic reticulum (ER) stress pathway is another potential mechanism through which IH contributes to oxidative stress in NAFLD. IH activates the ER stress pathway, leading to dysregulation of hepatocyte lipid homeostasis and subsequent accumulation of toxic lipids. This triggers ER stress and activates the unfolded protein response (UPR), which is a physiological mechanism for maintaining protein folding homeostasis.⁴⁹ However, excessive UPR activation can result in pathological conditions, including hepatocellular damage and apoptosis.^{56–58} Tauroursodeoxycholic acid (TUDCA), a bile acid derivative used for treating cholelithiasis and cholestatic liver diseases, plays a crucial role in enhancing protein folding to alleviate ER stress.^{59–61} A previous animal study demonstrated that IH induces ER stress, leading to elevated levels of tumor necrosis factor and interleukin-1 β in hepatic tissues, ultimately leading to hepatic injury. However, TUDCA exhibited a protective effect on the liver against IH-induced injury and apoptosis by effectively inhibiting ER stress.⁶² Despite these findings, the specific mechanism underlying IH-induced UPR in NAFLD development remains unclear. Understanding how IH-induced UPR contributes to the pathogenesis of NAFLD could provide valuable insights into potential therapeutic targets. Further investigations on the intricate interplay among IH, ER stress, and NAFLD development could contribute to the development of novel treatment strategies for this complex liver condition.

IH and Dyslipidemia

NAFLD is characterized by the excessive accumulation of fat in the liver, with disturbances in hepatic and systemic lipid metabolism identified as key pathological mechanisms.⁶³ Interestingly, there is increasing evidence demonstrating that OSA is a risk factor for various metabolic disorders due to sleep disturbance and IH, particularly affecting lipid metabolism. OSA and dyslipidemia exhibit a strong bidirectional relationship.^{2,64–67} OSA and IH appear to play pivotal roles in NAFLD development by enhancing adipose tissue lipolysis, leading to increased availability of free fatty acids (FFAs) in the serum, promoting hepatic biosynthesis, delaying postprandial lipid clearance, and reducing mitochondrial fat oxidation (FAO).⁶⁸ Severe sleep apnea has been reported to increase FFA levels during sleep in patients with heart failure, a phenomenon prevented by supplemental oxygen.⁶⁹ Plasma FFA levels were also found to be increased during sleep in OSA patients without heart failure, with CPAP attenuating lipolysis. Additionally, CPAP withdrawal in OSA patients leads to increased

FFA levels, associated with increased sympathetic and adrenocortical activities.⁷⁰ Animal models further support the role of IH in dyslipidemia and abnormal liver lipids. Mice, including lean mice, exposed to IH exhibited increased levels of serum cholesterol and other lipids. However, this effect was not observed in obese mice, potentially due to baseline hypercholesterolemia masking the effects of IH on lipid metabolism.^{71,72} IH appears to cause hepatic lipid biosynthesis by upregulating lipid biosynthesis genes, including sterol regulatory element-binding protein 1, stearoyl-coenzyme A desaturase 1, and fatty acid translocase CD36 (which facilitates FFA uptake in the liver) in mice.^{73–76} Moreover, IH may contribute to hyperlipidemia by affecting lipid clearance, reducing triglyceride (TG)-rich lipoprotein clearance, and inhibiting lipoprotein lipase activity in adipose tissues.⁷⁷ These factors collectively contribute to increased serum lipid levels and metabolic burden on the liver, ultimately resulting in hepatic fat accumulation, dyslipidemia, and steatohepatitis.

HIFs, particularly HIF-2 α , appear to play a crucial role in the hepatic lipid metabolism abnormalities induced by IH in NAFLD. Levels of CD36, a molecule involved in lipid transport, are significantly elevated in the livers of patients with OSA compared to controls, showing a positive correlation with key respiratory parameters such as AHI and oxygen desaturation index, which are well-known indicators of OSA severity.⁷⁴ Another study observed high expressions of both HIF-2 α and CD36 in the livers of NAFLD patients. Knockdown of CD36 in hypoxic liver cells notably reduced lipid accumulation, whereas knockdown of HIF-2 α reduced both lipid accumulation and CD36 expression. Additionally, mice deficient in HIF-2 α exhibited decreased CD36 levels and improved NASH characteristics.⁷⁸ These findings strongly support the role of HIF-2 α in hepatic lipid accumulation by regulating CD36 expression and function. Furthermore, hypoxia-induced overexpression of HIF-2 α suppressed peroxisome proliferator-activated receptor (PPAR) in steatotic human hepatocytes (L02 cells) treated with FFAs and in a high-fat diet (HFD)-fed mouse model of NAFLD. This resulted in IR, suppression of fatty acid β -oxidation, or increased lipogenesis, exacerbating NAFLD progression. However, these effects were mitigated by HIF-2 α silencing or PPAR α activation.⁷⁹ Interestingly, oxygen therapy, involving treatment of HFD-fed mice with 88% oxygen concentration and palmitic acid (PA)-treated primary hepatocytes with 100% oxygen concentration for 1 h twice daily, alleviated hepatic steatosis by inhibiting hepatic de novo lipogenesis. This was achieved by reducing HIF-2 α expression (but not HIF-1 α) and improving glucose metabolism and insulin sensitivity.⁸⁰ These findings collectively suggest that IH exacerbates NAFLD progression by inducing HIF-2 α expression.

The role of HIF-1 α in lipid metabolism in NAFLD is also noteworthy. In a choline-deficient diet-induced NAFLD mouse model, livers deficient in HIF-1 α exhibited more pronounced steatosis and increased TG accumulation compared to wild-type livers.⁸¹ However, despite its importance, HIF-1 α is considered dispensable in NAFLD development. Both HIF-1 α and HIF-2 α are significantly activated in primary hepatocytes treated with cobalt chloride (CoCl₂), a hypoxic inducer simulating HIF effects, or cultured in a 1% O₂ environment. However, neither palmitate acid- nor hypoxia-induced hepatic steatosis improved with siHIF-1 α or siHIF-2 α treatments, respectively, suggesting the involvement of an HIF-independent pathway in hepatic steatosis.⁸² Additionally, IH exacerbates liver fibrosis in hepatocyte-specific deletion of HIF-1 α (Hif1 α -/-),⁸³ implying that the role of IH in liver fibrosis may extend beyond its direct effect on HIF-1 α . In conclusion, the intricate relationship among OSA, IH, and NAFLD involves dysregulated lipid metabolism and the pivotal role of HIFs, particularly HIF-2 α . Further research is needed to unravel the complex interplay between IH, HIFs, and alternative pathways contributing to the pathogenesis of NAFLD.

IH and Insulin and/or Leptin Resistance

Leptin plays a crucial role in reducing food intake and increasing energy expenditure, whereas insulin is essential for metabolizing ingested nutrients, particularly glucose. However, insulin and/or leptin resistance, characterized by impaired insulin and/or leptin action, are strongly implicated in NAFLD development.^{84–88} Several factors contribute to the specific role of IR in the pathological mechanisms of NAFLD.^{89–91} First, IR increases the breakdown of peripheral adipose tissues, elevating FFA levels in the bloodstream, which then enter the liver. Second, IR leads to a compensatory increase in insulin synthesis and secretion by pancreatic β -cells, resulting in hyperinsulinemia and increased de novo fat synthesis in the liver. Finally, IR causes adipose tissue dysfunction and abnormal adipokine secretion, resulting in elevated IL-6 and TNF- α levels.

Interestingly, many epidemiological studies have indicated a strong association between OSA and insulin and/or leptin resistance.^{92–94} In rats, exposure to IH may contribute to the induction of a state of insulin and/or leptin resistance, potentially leading to increased food intake and weight gain.⁶⁵ There are several plausible mechanisms through which IH leads to IR.^{93,95–97} First, hypoxia affects the phosphorylation of insulin receptor tyrosine kinase, reducing the effectiveness of insulin receptors. Additionally, hypoxia activates the sympathetic nervous system and peripheral chemoreceptors, resulting in increased adrenaline and glucocorticoid levels, which antagonize the biological effects of insulin. Moreover, hypoxia induces oxidative stress and upregulates the expression of inflammatory factors, contributing to IR. IH may mediate IR through inflammatory remodeling of adipose tissue independent of obesity.^{93,98} A possible molecular mechanism involves IH triggering the production of multiple inflammatory mediators through the activation of downstream NF- κ B pathways, including TNF- α and C-C motif chemokine ligand 2, which play roles in the development and perpetuation of IR and chronic adipose tissue inflammation.^{99,100} Additionally, IH can promote TNF- α , IL-1 β , and IL-6 production by activating the MAPK signaling pathway, leading to inflammation and cell apoptosis.¹⁰¹ Moreover, IH can result in abnormal expression and secretion of cytokines from cells, including hepatokines, adipokines, and myokines, further exacerbating IR.⁹⁷ For example, selenoprotein P, a hepatokine associated with the development of IR, was found to be upregulated by IH via a microRNA-203-mediated mechanism.^{102,103} In summary, a close relationship among OSA, IR, and NAFLD is plausible.

Numerous studies have shown that OSA/IH is associated with the development of NAFLD through the induction of IR.^{104–106} In one study, the HOMA-IR index was independently associated with NAFLD in patients with OSA, even after adjusting for confounders.^{104,105} Another study indicated that AHI and HOMA-IR index were independent risk factors for elevated ALT levels in obese NAFLD patients with OSA.¹⁰⁶ In conclusion, the induction of insulin and/or leptin resistance may serve as a critical link between OSA and NAFLD development. However, the specific molecular mechanisms remain unclear, and exploring the effects of IH on inflammatory molecules and pathways may offer valuable insights into understanding IR.

IH and Gut Microbiota

The balanced gut microbiota plays critical physiological roles in the host immune system, normal gut–liver circulation, and metabolism.^{107,108} Accumulating evidence suggests that gut dysfunction, particularly dysbiosis and alterations in gut metabolites, may contribute to NAFLD development and progression.^{109,110} Furthermore, gut microbial composition is associated with NAFLD severity and outcomes.^{111–114} Several studies have reported that both obese and nonobese NAFLD patients exhibit fecal dysbiosis and distinct microbial community compositions compared to controls, including bacteria, fungi, and viruses.^{111,115–119} It appears that gut microbiota dysbiosis significantly impacts NAFLD, irrespective of obesity.^{116,119} Furthermore, regulating the gut microbiome may represent a therapeutic target in NAFLD.^{120–124} Several plausible mechanisms explain how gut microbiota may influence NAFLD progression. Briefly, dysbiosis leads to intestinal inflammation and gut barrier dysfunction, resulting in changes in the translocation of live bacteria and microbial products (including lipopolysaccharides [LPSs], trimethylamine N-oxide, short-chain fatty acids [SCFAs], bile acids, and ethanol) due to increased intestinal permeability. This promotes liver injury and inflammation.^{110,125–129} SCFAs produced by the gut microbiome have important effects on energy metabolism, immunity, and gut function regulation.^{130,131} The types and amounts of SCFAs are altered in NAFLD.¹¹⁰ LPS activation of toll-like receptors (TLRs) and inflammasomes also contributes to the pathological mechanism.¹³² Fecal microbiota transplantation from healthy donors has been shown to reduce small intestinal permeability, highlighting the role of gut microbiota in NAFLD.¹³³ Additionally, there are several clinical trials investigating drugs that regulate bile acid synthesis in NAFLD.^{134,135}

There is increasing evidence indicating an association between OSA and altered gut microbiota. Although animal models have demonstrated that IH, SF, intermittent hypercapnia, or sleep deprivation (which OSA can cause) lead to dysbiosis,^{136–142} data on changes in gut microbiota in OSA patients are limited. Two pediatric studies have shown altered gut microbiota function and composition,¹⁴³ decreased microbiota diversity, and increased inflammation.¹⁴⁴ Another study revealed gut microbial dysbiosis in OSA patients, characterized by changes in gut function, reduction in SCFA-producing bacteria, and increased pathogen levels along with elevated IL-6 levels.¹⁴⁵ Additionally, alterations in gut microbiota and glucometabolic changes have been observed in healthy young individuals with recurrent partial sleep

deprivation.¹⁴⁶ This suggests that OSA contributes to the development and progression of NAFLD by inducing gut microbiota dysbiosis, which in turn could promote intrahepatic and systemic inflammation.^{147,148} Moreover, OSA-associated changes in gut microbiota have been implicated in the development of type 2 diabetes mellitus and exacerbation of outcomes in coronavirus disease 2019 by promoting systemic inflammation.^{149,150} Interestingly, a study found that OSA with the *Prevotella* enterotype (*Prevotella*-dominated gut microbiomes) significantly disrupted arousal-related parameters or sleep stages.¹⁵¹ Notably, NASH microbiomes are often categorized into the *Prevotella* enterotype, whereas healthy microbiomes are less represented by *Prevotella*.¹⁵² This indicates a potential mechanism underlying the association between OSA and NAFLD. However, studies on the abundance of *Prevotella* in patients with OSA or NAFLD have yielded inconsistent results,^{109,112,145,152} possibly due to small sample sizes or variations among regions and ethnic groups. Therefore, further studies on the composition of microbial communities in OSA and NAFLD are warranted.

However, relatively little is known about how OSA induces gut microbiota involvement in NAFLD development and progression. An increase in LPSs due to impaired gut barrier function leads to the activation of TLRs, which are crucial in liver inflammation and fibrosis.^{148,153,154} One study highlighted the prominence of low-level endotoxemia and systemic inflammation in obese children with OSA.¹⁴⁷ Moreover, another study monitoring sleep and related indices in 80 children with biopsy-proven NAFLD revealed that OSA (defined as AHI ≥ 1) is associated with increased endotoxemia, impaired gut barrier function, increased TLR-4-mediated hepatic susceptibility to endotoxemia, and expansion of the adiponectin-deficient hepatic progenitor cell pool.¹⁴⁸ However, the study focused on children and had a relatively small sample size. It should be noted that the definition of OSA in children (AHI ≥ 1) slightly differs from that in adults. Several potential mechanisms underlie how gut microbiota links OSA to NAFLD. In short, IH- or SP-induced changes in the gut microbiome lead to increased intestinal permeability, gut barrier dysfunction, and an increase in harmful microbial metabolites, as discussed above. This, in turn, promotes the translocation of live bacteria and microbial products, ultimately contributing to liver inflammation and fibrosis.^{92,109,148} Additionally, alterations in the gut microbiota induced by IH or SF also contribute to other pathological changes, including IR and lipid metabolism, as previously discussed, further exacerbating the development and progression of NAFLD.

In summary, existing evidence does not conclusively establish whether the gut microbiota is truly involved in the association between OSA and NAFLD. This review provides a conceptual framework, but further clinical evidence and foundational research are necessary to confirm the role of gut microbiota in OSA-associated NAFLD. Importantly, compelling evidence demonstrating the efficacy of targeting the gut microbiota to mitigate NAFLD progression mediated by IH is required. Continued research into the intricate interplay among OSA, gut microbiota, and NAFLD will contribute to a more comprehensive understanding of their associations, transitioning from speculative theories to evidence-based conclusions.

IH and Cell Death

It is well established that hepatocyte injury and death contribute to NAFLD pathology. Although apoptosis and necrosis have been shown to be the dominant drivers of progression and fibrosis,^{155,156} more recently, other types of cell death, including necroptosis, pyroptosis (inflammatory programmed cell death), and ferroptosis,^{155–159} have also been recognized to play important roles in NAFLD progression. However, autophagy, which maintains cellular homeostasis, plays a dual role in NAFLD. Autophagy plays a protective role in hepatocytes, whereas defects in autophagy in the endothelial cells of the liver in NAFLD patients promote liver inflammation and fibrosis.^{160,161} In contrast, autophagy is detrimental to hepatic stellate cells, thereby promoting liver fibrosis.¹⁶²

Increasing evidence suggests that OSA promotes hepatocyte injury and death via IH, contributing to NAFLD development.^{30,148,163–167} In children with NAFLD and OSA, the duration of hemoglobin desaturation ($<90\%$) was associated with increased levels of circulating markers of hepatocyte apoptosis and fibrogenesis.^{30,148} In NAFLD animal models, IH can exacerbate hepatocyte apoptosis to ameliorate liver inflammation and injury via ER and oxidative stress, which can be reversed by ammonium pyrrolidine dithiocarbamate (a scavenger of ROS), *Lactobacillus rhamnosus* GG culture supernatant (improving lipid metabolism by increasing circulating adiponectin levels), or 4-phenylbutyric acid.^{164,165,168} Additionally, OSA is implicated in necroptosis in NAFLD, a programmed cell death mechanism triggering inflammation by receptor-interacting protein kinase-3 (RIPK3) and mixed-lineage kinase domain-like pseudokinase (MLKL). IH appears to exacerbate

oxidative stress and inflammation by promoting PA-induced necroptosis in liver LO2 cells and high-fat choline-deficient mice. Liver injury is significantly reduced by blocking the function of RIPK3 to induce necroptosis or TBHQ (an activator of Nrf2 to reduce oxidative stress).¹⁶⁷ Moreover, Nrf2 dysregulation is associated with hepatic ferroptosis, inducing CIH-induced liver injury in rats.¹⁶⁹ Furthermore, melatonin can enhance autophagy to prevent IH-exacerbated hepatocellular damage by activating SIRT1-mediated autophagy signaling in an HFD-fed mouse model.¹⁷⁰ However, CIH can increase hepatic steatosis and ER stress by promoting the dysregulated activity of hepatic autophagy, implying the involvement of IH in NAFLD development by mediating autophagy dysregulation.¹⁷¹ HIF-1 α may be a driver of cell death in NAFLD patients with OSA. One study found that CoCl₂ exacerbated FFA-induced TG levels and higher cell death rates by promoting inflammatory signals, including NLRP3 inflammasome/caspase-1 activation,¹⁶³ which contributes not only to pyroptosis but also to apoptosis, necroptosis, and ferroptosis.¹⁷² In conclusion, OSA promotes various types of cell death in NAFLD progression via IH; however, considering the crosstalk and/or overlap between different cell death pathways, pan-cell death, such as PANoptosis,¹⁷³ but not a single cell death, is likely to play a role in NAFLD. Future research should explore the role of PANoptosis in NAFLD.

Possible Markers

The diagnosis of OSA through PSG and the definitive diagnosis of NAFLD via liver biopsy both present significant challenges. PSG, although considered the gold standard for OSA diagnosis, is a complex and often expensive procedure that requires overnight monitoring in a sleep laboratory. On the other hand, liver biopsy, the gold standard for diagnosing NAFLD, involves an invasive procedure with potential risks and discomfort for the patient. Given these challenges, there is a pressing need for simpler and more accessible diagnostic tools for both OSA and NAFLD, enabling quicker and less invasive diagnosis. This would facilitate earlier intervention and lead to better patient outcomes.

Table 1 provides a comprehensive overview of the current state of research on markers for OSA and NAFLD. These markers span various categories, including polysomnographic parameters, genomics, inflammatory proteins, proteomics, and metabolomics.

Table 1 Possible Screening Markers for OSA and NAFLD Patients

Type	Name	References	Possible Significance
PSG parameters	LaSO ₂	[104,105,174,177–179]	Mean SaO ₂ % may predict patients with obesity and OSA and those at a higher risk of developing advanced fibrosis; AHI was significantly correlated with lobular inflammation and fibrosis; the others may be predictors of NAFLD among OSA patients.
	Mean SaO ₂ %	[174–176]	
	TS90	[104,177]	
	ODI	[104,174,180]	
	AHI	[22,106,177,178]	
Genomics	Snoring index	[181]	Associated with an increased risk of OSA and NAFLD development.
	The allele Gly972Arg	[182]	
	Polymorphism of IRS1, CRP, IL-6, and LEPR	[183]	
Proteomics	LOX	[184]	May serve as a biomarker for liver fibrosis in OSA.
Metabonomics	TG	[105]	May predict NAFLD development.
	HOMA-IR	[104–106]	
Inflammatory markers	Leptin, adiponectin	[185]	Associated with an increased risk of OSA and NAFLD.
	MIF, IL-6	[185]	
	Hs-CRP	[106,185]	
	TNF- α	[185]	
Others	BMI	[105,178,186]	BMI may predict the development of NAFLD and OSA; FLI and HSI may serve as good screening tools for detecting NAFLD in OSA patients.
	FLI	[27,187,188]	
	HSI	[187]	

Abbreviations: PSG, polysomnographic; LaSO₂, lowest oxygen saturation; Mean SaO₂%, mean percentage oxyhemoglobin; TS90, total sleep time spent with oxygen saturation of <90%; ODI, oxygen desaturation index; AHI, apnea/hypopnea index; IRS1, insulin receptor substrate 1; CRP, C-reactive protein; IL-6, interleukin-6; LEPR, leptin receptor; LOX, lysyl oxidase; TG, triglyceride; HOMA-IR, homeostatic model assessment for insulin resistance; MIF, macrophage migration inhibitory factor; Hs-CRP, highly sensitive C-reactive protein; TNF- α , tumor necrosis factor alpha; BMI, body mass index; FLI, fatty liver index; HSI, hepatic steatosis index.

metabolism-related markers, and liver imaging indices. Among these markers, PSG parameters serve as indicators of OSA severity and may be pivotal in assessing the severity of NAFLD. For instance, mean SaO₂% has been linked to predicting obese and OSA patients who are at a higher risk of advanced fibrosis,^{174–176} whereas AHI is significantly correlated with lobular inflammation and fibrosis.^{22,106,177,178} This also suggests that significant abnormalities in PSG parameters in OSA patients warrant attention to the health of their liver.

Some metabolic and inflammatory markers, such as TGs, TNF- α , and IL-6, may also have diagnostic value for OSA and NAFLD;^{105,185} however, it is important to note their lack of specificity. Nevertheless, certain biomarkers may hold particular significance for guiding the diagnosis of OSA and NAFLD. For example, a study involving 35 patients with severe obesity who underwent liver biopsy, PSG, and serum lysyl oxidase (LOX) testing found that AHI was elevated in patients with fibrosis. LOX, an enzyme involved in cross-linking collagen levels, also showed elevated serum levels in patients with evidence of hepatic fibrosis. Moreover, patients with severe OSA exhibited higher baseline LOX levels compared to healthy controls. These findings suggest that LOX serves as a biomarker of liver fibrosis in patients with severe obesity, OSA, and NAFLD.¹⁸⁴ Additionally, a study involving 431 newly diagnosed OSA patients found that the fatty liver index and hepatic steatosis index values were significantly elevated in the NAFLD group, indicating their potential use as screening tools for NAFLD in adults with obstructive sleep apnea/hypopnea syndrome.¹⁸⁷ However, the clinical significance of these markers requires further investigation. It is necessary to expand sample sizes and adopt more rigorous research designs to explore the diagnostic value of these markers for OSA and NAFLD.

In conclusion, although each marker may have its strengths and limitations, combining multiple markers into predictive models could enhance diagnostic accuracy and provide valuable insights into disease progression. In the future, simpler and more effective diagnostic methods are needed to diagnose and treat OSA or NAFLD earlier. Additionally, identifying individuals at high risk of developing OSA-related complications, including NAFLD, is crucial such that treatment efforts can be appropriately focused on them.

Discussion and Outlook

HIFs play a critical role in the pathological state induced by OSA, and controlling disease progression may involve intervening in the excessive activation of downstream pathways regulated by HIFs. However, the HIF signaling pathway also plays a crucial role in various molecular and signaling pathways. Effectively targeting HIFs or their downstream key molecules in NAFLD patients with OSA while minimizing potential side effects poses a significant challenge and remains a key focus for future research.

The proportion of OSA patients with NAFLD or vice versa is not clearly defined; hence, large-scale epidemiological studies are necessary to elucidate this relationship. Moreover, NAFLD and OSA may exacerbate each other, forming a vicious cycle. Therefore, based on existing evidence, clinicians must remain vigilant regarding the coexistence of these conditions and raise awareness about the potential complications of OSA. Timely screening for OSA is crucial for diagnosis, especially considering that many snorers may not exhibit severe symptoms and thus overlook the chronic metabolic risks associated with OSA. The efficacy of CPAP in treating OSA combined with NAFLD remains uncertain. Therefore, further exploration of appropriate inclusion criteria, outcome indicators, observation time, and standardized CPAP treatment protocols is necessary to determine the exact effect of CPAP. Additionally, combining CPAP with other weight loss methods, such as exercise, may enhance its effectiveness in improving OSA and its comorbidities, including NAFLD. Clinicians should recognize the close relationship between OSA and metabolic diseases and provide management education, including guidance on increased exercise and weight loss, particularly for individuals with NAFLD and those who are obese. However, further studies are needed to investigate the causal relationship between OSA and NAFLD and elucidate their underlying mechanisms to develop more effective treatment strategies.

Conclusion

Although confounding factors, such as obesity, have introduced significant complexity into the study of OSA and metabolic diseases, increasing evidence indicates that OSA is independently involved in the development of NAFLD. OSA mediates systemic or local inflammation and oxidative stress, primarily through IH and SF, leading to disturbances in glucose and lipid metabolism, dysregulation of the gut microbiome, various modes of cell death, and ultimately, the

development of NAFLD. It is important to note the substantial interplay between the risk factors for NAFLD and OSA, making it challenging to discern cause and effect. Clarifying the relationship between NAFLD and OSA represents a long and arduous journey.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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